

Supplementary Information

Variants near *TERT* and *TERC* influencing telomere length are associated with high-grade glioma risk

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Supplementary Table 1. Subject characteristics of high-grade astrocytic glioma patients and controls, the University of California, San Francisco (UCSF) Bay Area Adult Glioma Study (AGS) 1997-2011, Illumina iControls, The Cancer Genome Atlas (TCGA) glioblastoma patients, Wellcome Trust (WTCCC) controls and Mayo Clinic and UCSF replication samples.

Populations	N (cases/cntrls)	Phase of study	Histologies	TERC genotyping technique	Ethnicity	% Female (cases/cntrls)	Median Age (cases/cntrls)
UCSF Adult Glioma Study	620 / 602	Discovery (Stage 1)	Glioblastoma (85%) ^a	Illumina 370k	Caucasian	36% / 47%	56 / 57
TCGA glioblastoma cases	70 / 0	Discovery (Stage 1)	Glioblastoma	Illumina 550k	Caucasian	43% / -	55 / -
Illumina iControls	0 / 3390	Discovery (Stage 1)	-	Illumina 300k/370k/550k	Caucasian	- / 63%	- / 31
TCGA glioblastoma cases	323 / 0	Discovery (Stage 2)	Glioblastoma	Affymetrix 6.0	Caucasian	38% / -	60 / -
Wellcome Trust controls	0 / 2603	Discovery (Stage 2)	-	Affymetrix 6.0	Caucasian	- / 48%	- / - ^c
UCSF replication	303 / 375	Replication (Stage 3)	Glioblastoma	TaqMan genotyping (96%) ^b	Caucasian	35% / 43%	57 / 58
Mayo replication	328 / 766	Replication (Stage 3)	Glioblastoma	TaqMan genotyping	Caucasian	37% / 43%	56 / 49

^a 15% of the high-grade glioma samples were Grade 3 anaplastic astrocytomas

^b A total of 25 samples were genotyped using a Sequenom custom panel

^c Precise age data was unavailable for these publically available controls. It should be noted that >50% of the included samples from the WTCCC were members of the 1958 UK Birth Cohort.

Supplementary Table 2: Association between new and previously established glioma risk alleles and mean leukocyte telomere length (LTL) in a genome-wide association study from the ENGAGE Consortium Telomere Group (Codd *et al.*, 2013).

Glioma risk SNP	Position	Putative gene	Alleles ¹	RAF ²	Association with leukocyte telomere Length			
					N	Beta ³	SE	P-value
rs1920116	3: 169579971	<i>TERC</i>	G/A	0.71	37486	0.0733	0.0080	5.46x10 ⁻²⁰
rs2736100	5: 1286516	<i>TERT</i>	C/A	0.49	25842	0.0783	0.0087	4.39x10 ⁻¹⁹
rs2252586	7: 54978924	<i>EGFR</i>	A/G	0.29	37448	-0.0003	0.0078	0.972
rs11979158	7: 55159349	<i>EGFR</i>	A/G	0.82	34727	0.0157	0.0098	0.109
rs4295627	8: 130685457	<i>CCDC26</i>	G/T	0.19	37366	-0.0009	0.0091	0.924
rs1412829	9: 22043926	<i>CDKN2B</i>	G/A	0.44	37621	0.0056	0.0109	0.605
rs498872	11: 118477367	<i>PHLDB1</i>	A/G	0.31	32136	0.0010	0.0085	0.905
rs6010620	20: 62309839	<i>RTEL1</i>	G/A	0.77	37607	-0.0278	0.0085	1.1x10 ⁻³

¹ glioma risk allele is listed first

² RAF: risk allele frequency in GWAS of LTL

³ Beta estimates are for each additional copy of the glioma risk allele. Negative Beta values indicate the glioma risk allele is associated with shorter leukocyte telomere length, while positive Beta values indicate the glioma risk allele is associated with longer leukocyte telomere length).

N refers to the number of individuals meta-analyzed for telomere length association at each glioma-associated SNP. The sample size for rs2736100 is smaller than for other loci as this SNP is only present on certain genotyping platforms and, because of weak LD structure in the region, cannot be imputed reliably.

Supplementary Table 3: Genomic annotation by RegulomeDB, HaploRegV2 and Genevar for SNPs on 3q26.2 with p-values <0.01 in the glioma discovery meta-analysis of individuals from the UCSF AGS, TCGA and the WTCCC.

rsID	pos	LD ^a	EUR MAF ^a	GERP Cons ^b	RegulomeDB score ^c	Histone Marks ^d			eQTL ^f	Nearest Gene	Annotation	
						Promoter	Enhancer	DNase HS ^d				
rs12638862	3:169477506	0.31	0.26	No	5	.	5 cell types	.	.	TERC	Intergenic	
rs12630450	3:169480204	0.26	0.27	No	.	.	1 cell types	.	.	TERC	Intergenic	
rs12696304	3:169481271	0.26	0.27	No	5	1 cell type	3 cell types	.	RPC155	TERC	Intergenic	
rs2293607	3:169482335	0.4	0.25	No	4	8 cell types	1 cell type	4 cell types	14 proteins (e.g. POL2,TAF1, NFKB, CMYC)	TERC	Intergenic	
rs9822885	3:169486144	0.26	0.27	No	ACTRT3	Intronic	
rs9860874	3:169486271	0.26	0.27	No	6	ACTRT3	Intronic	
rs3821383	3:169489946	0.43	0.27	No	2b	8 cell types	1 cell type	5 cell types	14 proteins (e.g. BRCA1, IRF3, GATA2, NFKB)	MYNN	Intergenic	
rs10936599	3:169492101	0.48	0.25	Yes	5	3 cell types	6 cell types	5 cell types	.	MYNN	Synonymous	
rs3950296	3:169493283	0.48	0.25	No	5	.	4 cell types	.	.	MYNN	Intergenic	
rs1317082	3:169497585	0.48	0.25	No	6	MYNN	Intergenic	
rs3772190	3:169500487	0.48	0.25	No	6	MYNN	Intergenic	
rs1920120	3:169502180	0.43	0.27	No	6	MYNN	Intergenic	
rs2141595	3:169503432	0.43	0.27	No	MYNN	Intergenic	
rs1920122	3:169506141	0.43	0.27	No	MYNN	3' UTR	
rs13069553	3:169508272	0.48	0.25	No	5	.	.	2 cell types	.	MYNN	Intergenic	
rs7625734	3:169508915	0.43	0.27	No	3a	.	.	7 cell types	MAFK	MYNN	Intergenic	
rs7633750	3:169509244	0.43	0.27	No	5	.	.	2 cell types	.	MYNN	Intergenic	
rs1997392	3:169509652	0.43	0.27	No	LRRC34	Intergenic	
rs9868000	3:169510789	0.43	0.27	No	6	LRRC34	Intergenic	
rs7621631	3:169512145	0.47	0.26	No	LRRC34	Intronic	
rs10936600	3:169514585	0.48	0.25	Yes	LRRC34	Missense	
rs6793295	3:169518455	0.43	0.27	Yes	LRRC34	Missense	
rs3796145	3:169524862	0.48	0.25	No	5	LRRC34	Intronic	
rs10936601	3:169528449	0.43	0.27	No	5	.	.	1 cell type	.	LRRC34	Intronic	
rs9831661	3:169528523	0.43	0.27	No	5	.	.	1 cell type	.	LRRC34	Intronic	
rs9878797	3:169529958	0.051	0.43	No	4	6 cell types	1 cell type	11 cell types	.	LRRC34	Intronic	
rs9841443	3:169530076	0.22	0.42	No	2b	6 cell types	1 cell type	3 cell types	.	LRRC34	Intronic	
rs6793160	3:169535266	0.281	0.41	No	4	.	.	1 cell type	.	ACTRT3	LRRIQ4	Intergenic

rs10936602	3:169536637	0.75	0.26	No	5	<i>LRRIQ4</i>	Intergenic
rs7632991	3:169538612	0.75	0.26	No	5	1 cell type	.	1 cell type	<i>LRRIQ4</i>	Intergenic
rs1920119	3:169540397	1	0.41	No	5	1 cell type	.	3 cell type	.	.	.	<i>ACTRT3</i>	<i>LRRIQ4</i>	Synonymous
rs10936603	3:169545652	0.77	0.26	No	5	.	.	2 cell types	<i>LRRIQ4</i>	Intronic
rs7647824	3:169552381	0.79	0.26	No	<i>LRRIQ4</i>	Intronic
rs9833035	3:169553498	0.79	0.26	No	4	.	1 cell type	<i>LRRIQ4</i>	Intronic
rs4352416	3:169554084	0.79	0.26	No	2a	.	1 cell type	9 cell types	IRF4, PU1, YY1, POL2	.	.	.	<i>LRRIQ4</i>	Intronic
rs2421830	3:169554129	0.79	0.26	No	3a	.	1 cell type	3 cell types	IRF4, YY1, POL2, PU1	.	.	.	<i>LRRIQ4</i>	Intronic
rs9831336	3:169558373	0.81	0.26	No	.	.	1 cell type	<i>LRRC31</i>	Intronic
rs12492588	3:169558711	0.81	0.26	No	.	.	1 cell type	1 cell type	<i>LRRC31</i>	Intronic
rs12489230	3:169558821	0.81	0.26	No	.	.	1 cell type	1 cell type	<i>LRRC31</i>	Intronic
rs16854453	3:169559234	0.81	0.26	No	4	.	2 cell types	6 cell types	PAX5C20, PAX5N19, PBX3, TCF12	.	.	.	<i>LRRC31</i>	Intronic
rs6785618	3:169562797	0.81	0.26	No	<i>LRRC31</i>	Intronic
rs13074500	3:169565571	0.81	0.26	No	5	.	4 cell types	2 cell types	<i>LRRC31</i>	Intronic
rs11717389	3:169566247	0.81	0.26	No	6	<i>LRRC31</i>	Intronic
rs12485940	3:169567241	0.8	0.26	No	6	<i>LRRC31</i>	Intronic
rs16847897	3:169568116	0.96	0.29	No	<i>ACTRT3</i>	<i>LRRC31</i>	Intronic
rs4955676	3:169568492	0.96	0.29	No	4	.	.	1 cell type	MAFF, MAFK	.	.	.	<i>LRRC31</i>	Intronic
rs4955677	3:169568510	0.96	0.29	No	4	.	.	1 cell type	MAFF, MAFK	.	.	.	<i>LRRC31</i>	Intronic
rs6764267	3:169568670	0.54	0.42	No	5	.	.	.	MAFF, MAFK	.	.	.	<i>LRRC31</i>	Intronic
rs11709840	3:169570241	0.99	0.29	No	6	.	1 cell type	.	.	.	<i>ACTRT3</i>	<i>LRRC31</i>	Intronic	
rs11919269	3:169574465	0.99	0.3	No	5	<i>ACTRT3</i>	<i>LRRC31</i>	Intronic	
rs4955678	3:169574912	1	0.29	No	5	<i>ACTRT3</i>	<i>LRRC31</i>	Intronic	
rs1920116^g	3:169579971	1	0.29	No	4	.	1 cell type	4 cell types	ERALPHA_A, FOXA1	ACTRT3	LRRC31	Intronic		
rs7647589	3:169582223	0.55	0.43	No	5	.	1 cell type	1 cell type	.	.	<i>ACTRT3</i>	<i>LRRC31</i>	Intronic	
rs16854488	3:169590002	0.61	0.27	No	.	.	1 cell type	<i>LRRC31</i>	Intergenic	

^aLD and EUR minor allele freq are based on 1000 Genomes EUR data. LD is calculated as r^2 relative to rs1920116.

^bGenomic Evolutionary Rate Profiling (GERP) scores >2 were taken to indicate evolutionary constraint/genetic conservation

^cRegulomeDB scores: 2a, TF binding+matched TF motif+matched DNase Footprint+DNase peak; 2b, TF binding+any motif+DNase Footprint+DNase peak; 3a, TF binding+any motif+DNase peak; 4, TF binding+DNase peak; 5, TF binding or DNase peak; 6, other.

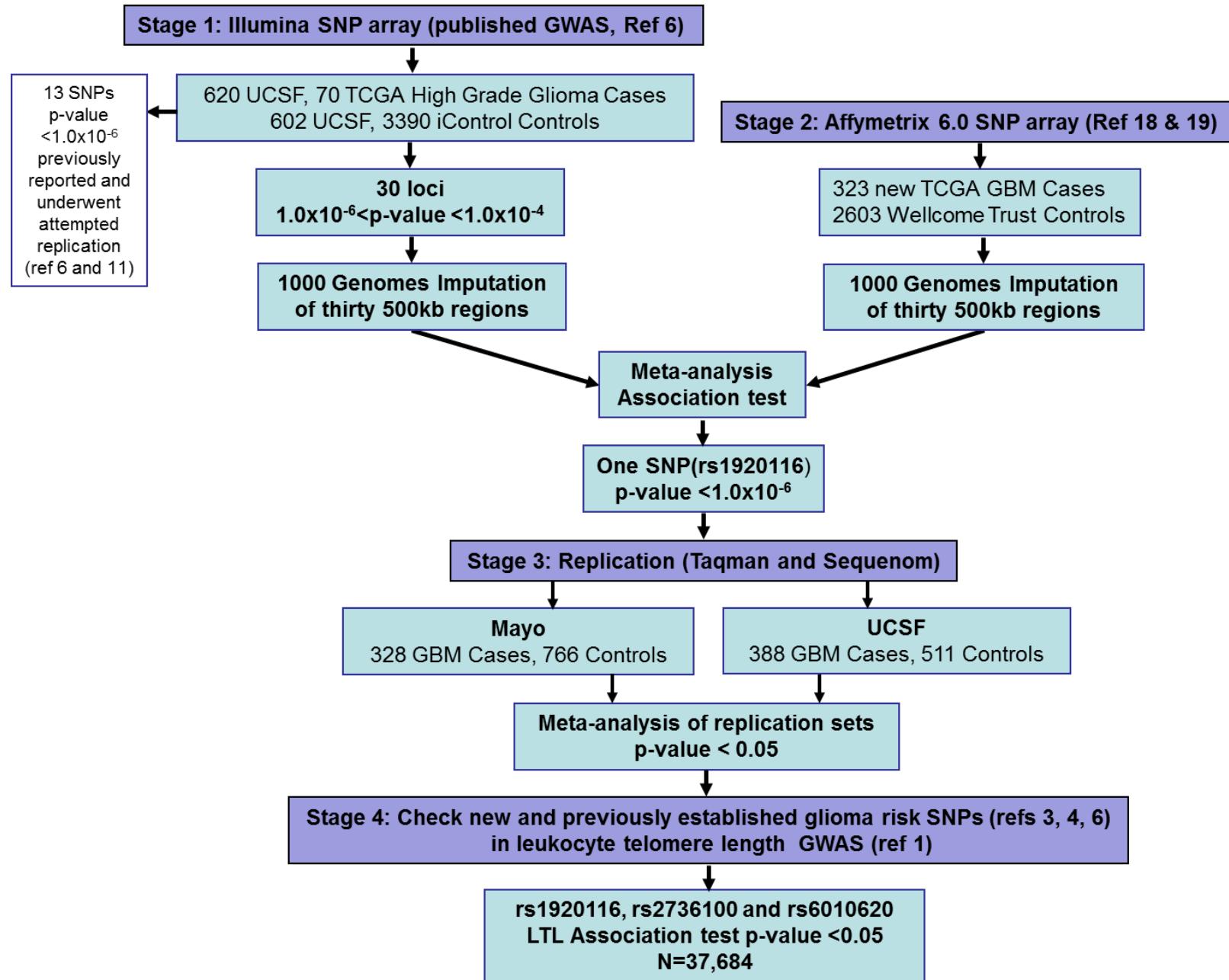
^dHistone Marks, DNase hypersensitivity sites and proteins bound by ChIP taken from ENCODE2 data

^eeQTL associations generated from Stranger, et al (2012) data analyzed using Spearman's rho with Genevar 3.3.0, restricted to Caucasian lymphoblastoid samples. A p-value cut-off of 0.05 was used.

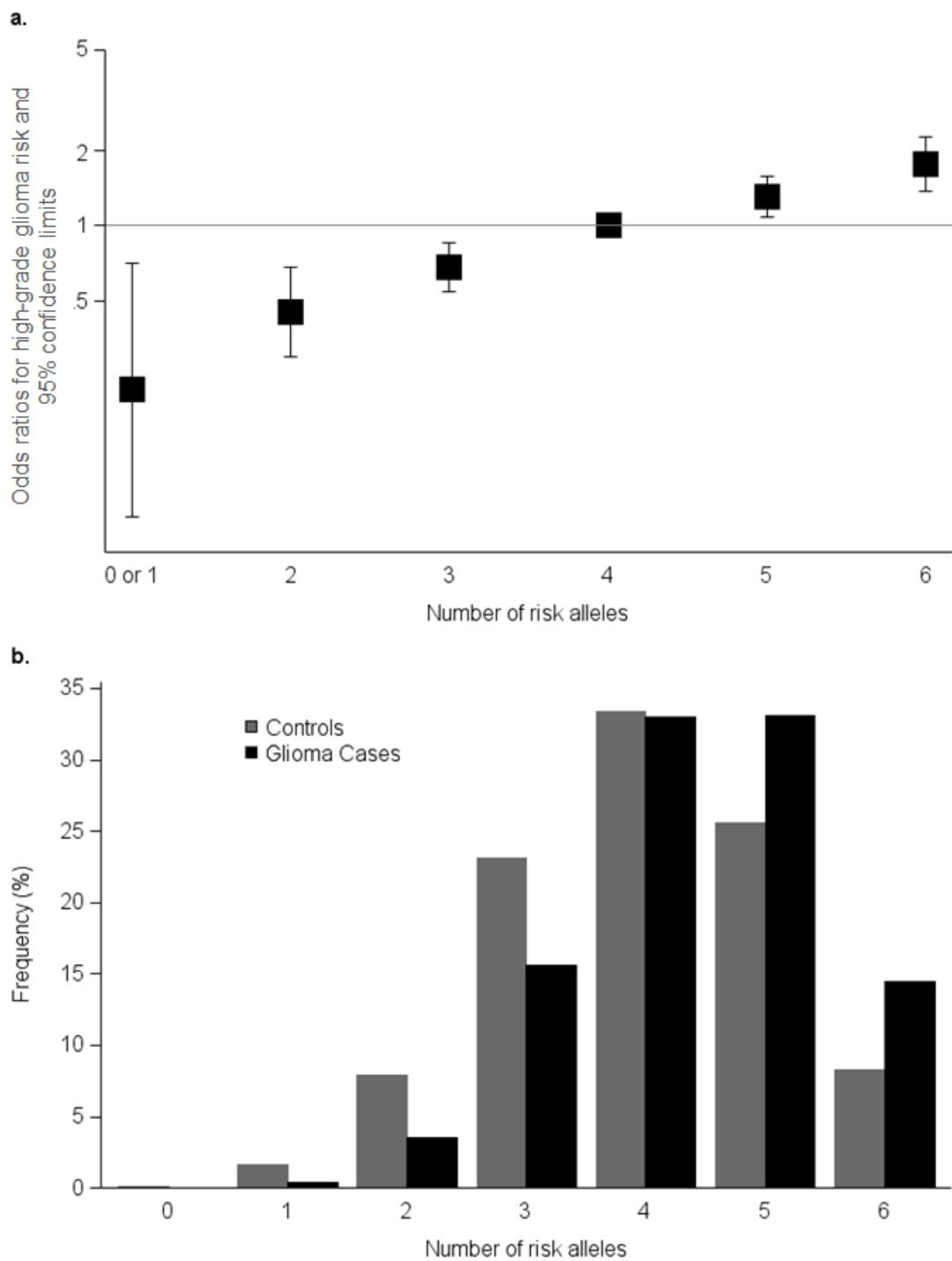
^gLead SNP from glioma analyses (rs1920116) appears in bold.

Supplementary Table 4: Lead SNPs from the original UCSF GWAS in thirty regions from Stage 1 analyses which merited follow-up analysis via imputation to 1000 Genomes and meta-analysis with TCGA and WTCCC samples.

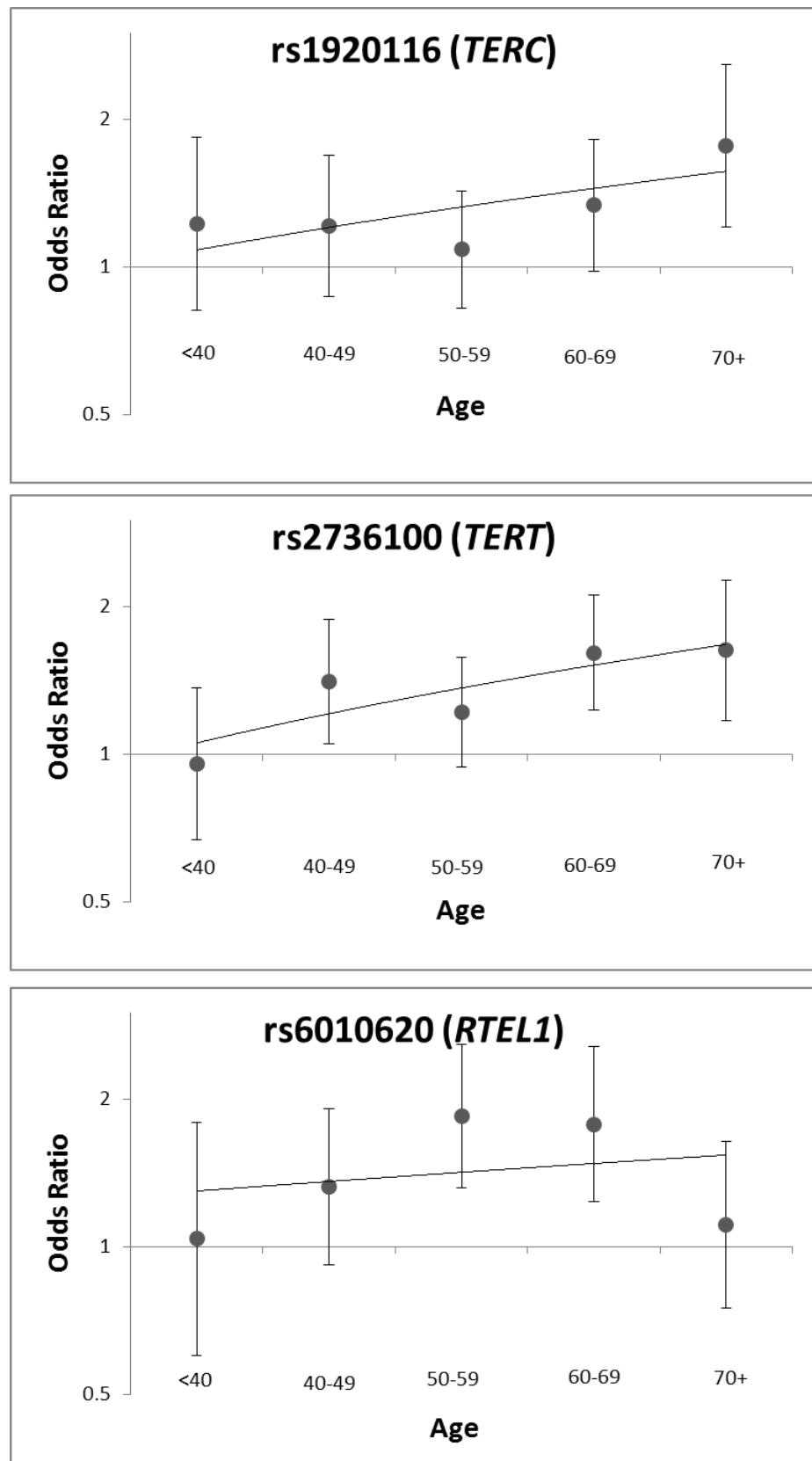
SNP	Chr	Pos(37)	Region Start	Region End	A1	A2	Gene	P (Stage1)
rs601344	1	60600945	60350945	60850945	A	G		5.62E-05
rs12995456	2	2594614	2344614	2844614	T	G		1.65E-05
rs714447	2	27028992	26778992	27278992	T	C		3.12E-05
rs2112040	2	45752214	45502214	46002214	A	G	<i>SRBD1</i>	4.27E-05
rs1878078	2	48318158	48068158	48568158	A	G		9.79E-06
rs10182802	2	206088211	205838211	206338211	A	G	<i>PARD3B</i>	5.83E-05
rs1920116	3	169579971	169329971	169829971	T	C	<i>LRRC31</i>	4.20E-06
rs219481	4	109340680	109090680	109590680	T	C		4.23E-05
rs2517552	6	31007590	30757590	31257590	A	G	<i>LOC729792</i>	9.20E-06
rs10484560	6	32298137	32048137	32548137	A	G	<i>C6orf10</i>	3.06E-05
rs1884043	6	47131174	46881174	47381174	T	C		2.90E-06
rs9359253	6	77872189	77622189	78122189	T	C		7.64E-05
rs11798	7	16899197	16649197	17149197	A	G	<i>AGR3</i>	7.04E-05
rs3779505	7	20405265	20155265	20655265	A	G	<i>ITGB8</i>	3.02E-06
rs202147	7	101650302	101400302	101900302	T	C	<i>CUX1</i>	6.98E-05
rs7781339	7	130985792	130735792	131235792	T	C		1.92E-05
rs4909443	8	139700911	139450911	139950911	A	G	<i>COL22A1</i>	9.16E-05
rs2797634	9	105640651	105390651	105890651	A	G		4.25E-05
rs12341266	9	116356516	116106516	116606516	A	G	<i>RGS3</i>	4.77E-06
rs2490059	10	28319692	28069692	28569692	A	G		7.81E-05
rs2758982	10	78065708	77815708	78315708	T	C	<i>C10orf11</i>	5.80E-05
rs498768	12	63759333	63509333	64009333	A	G		6.36E-05
rs10850707	12	117181708	116931708	117431708	T	C	<i>TMEM118</i>	8.39E-05
rs1011455	15	27293363	27043363	27543363	A	G	<i>GABRG3</i>	7.72E-05
rs968698	19	1263299	1013299	1513299	A	C		2.61E-05
rs3761034	19	18680478	18430478	18930478	A	C	<i>C19orf50</i>	6.32E-06
rs6066856	20	47396200	47146200	47646200	T	C	<i>PREX1</i>	5.91E-05
rs928844	21	37999799	37749799	38249799	T	C		5.06E-05
rs2839616	21	44425399	44175399	44675399	T	C	<i>PKNOX1</i>	5.75E-05
rs140040	22	36969932	36719932	37219932	A	G	<i>CACNG2</i>	7.64E-05



Supplementary Figure 1: Summary of Study Design and Analysis. The flowchart details flow of analyses through the 4 stages of the study



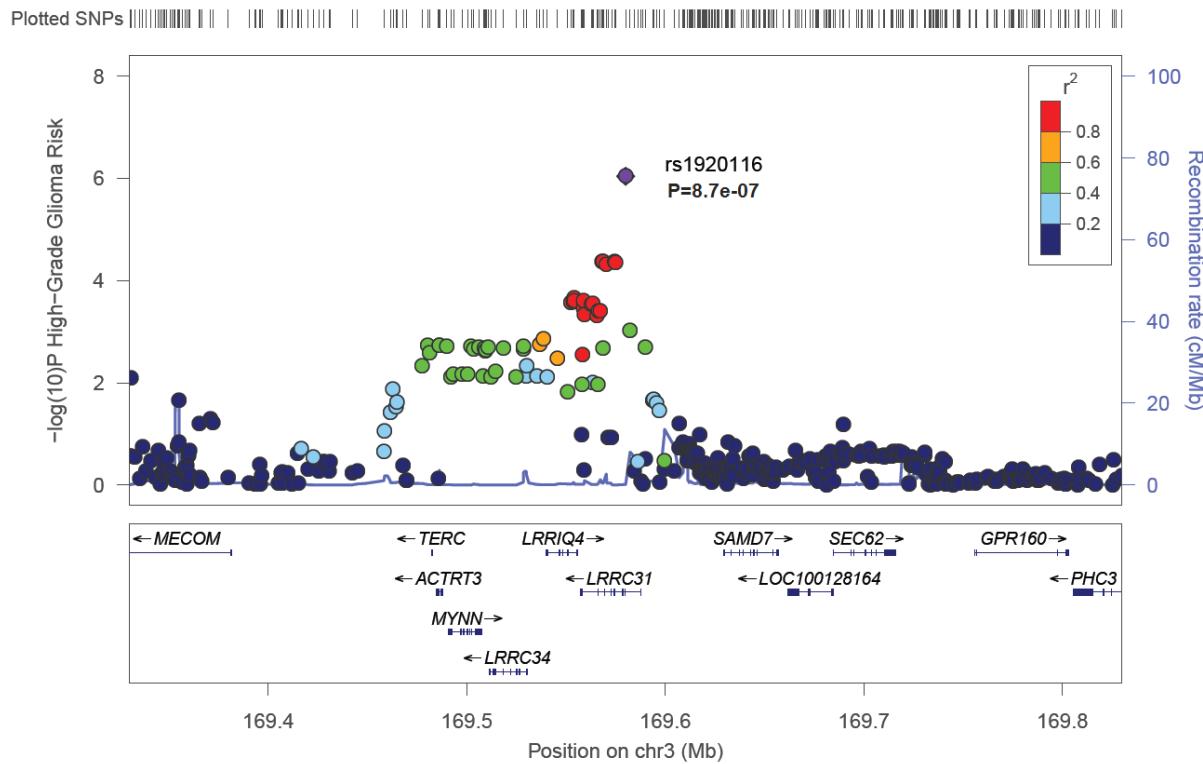
Supplementary Figure 2: Cumulative effect of three telomere-associated glioma risk SNPs (rs1920116, *TERC*; rs2736100, *TERT*; rs6010620, *RTEL1*). (A) Plot of the increasing ORs for high-grade glioma with increasing numbers of risk alleles (range 0-6). The ORs are relative to the median number of 4 risk alleles. Vertical bars correspond to 95% confidence intervals. Odds ratios increase in a monotonic fashion. **(B)** Distribution of telomere-associated glioma risk alleles in high-grade glioma cases (dark gray bars) and controls (light gray bars).



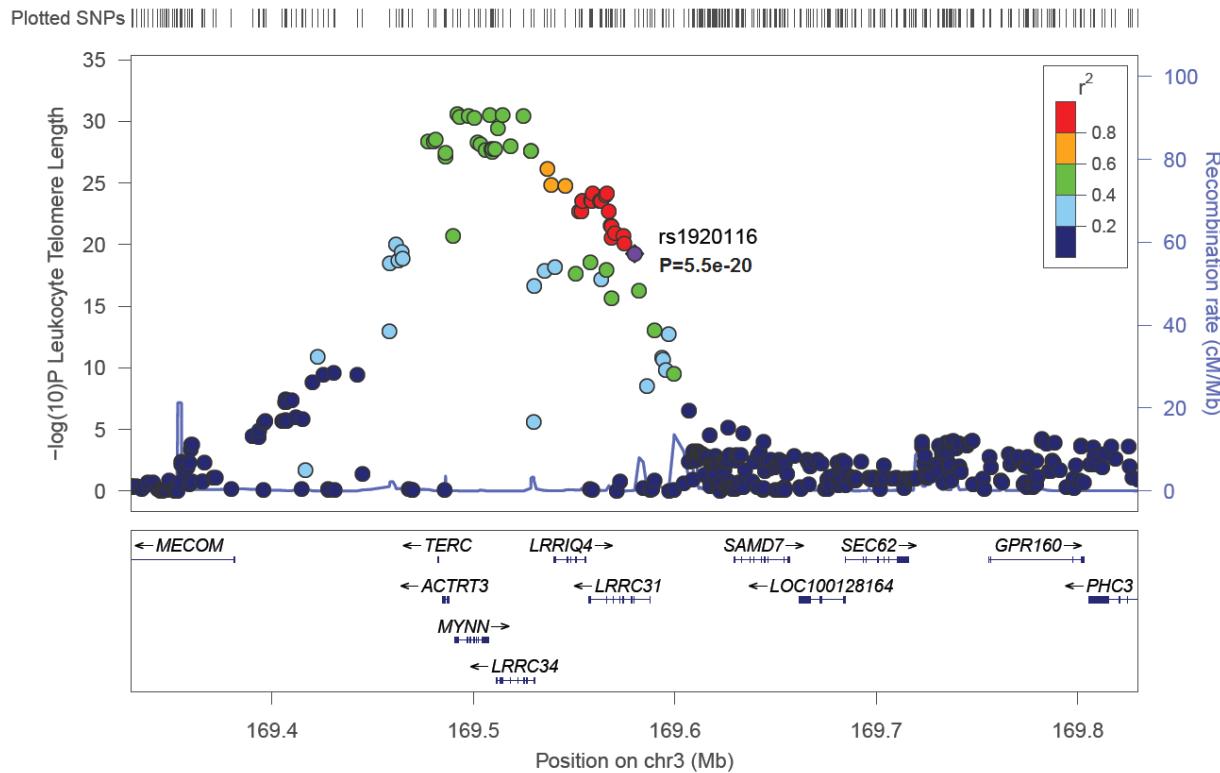
Supplementary Figure 3: Changes in the magnitude of high-grade glioma risk associated with telomere-associated SNPs across subject age strata in analyses of UCSF AGS cases and controls. Odds ratios for glioma were calculated in case-control analyses, adjusted for sex. The y-axis is represented on a log-scale (base 2), ranging from 0.50 to 2.0. Vertical bars correspond to 95% confidence intervals.

a

Chr3 High-Grade Glioma Associations



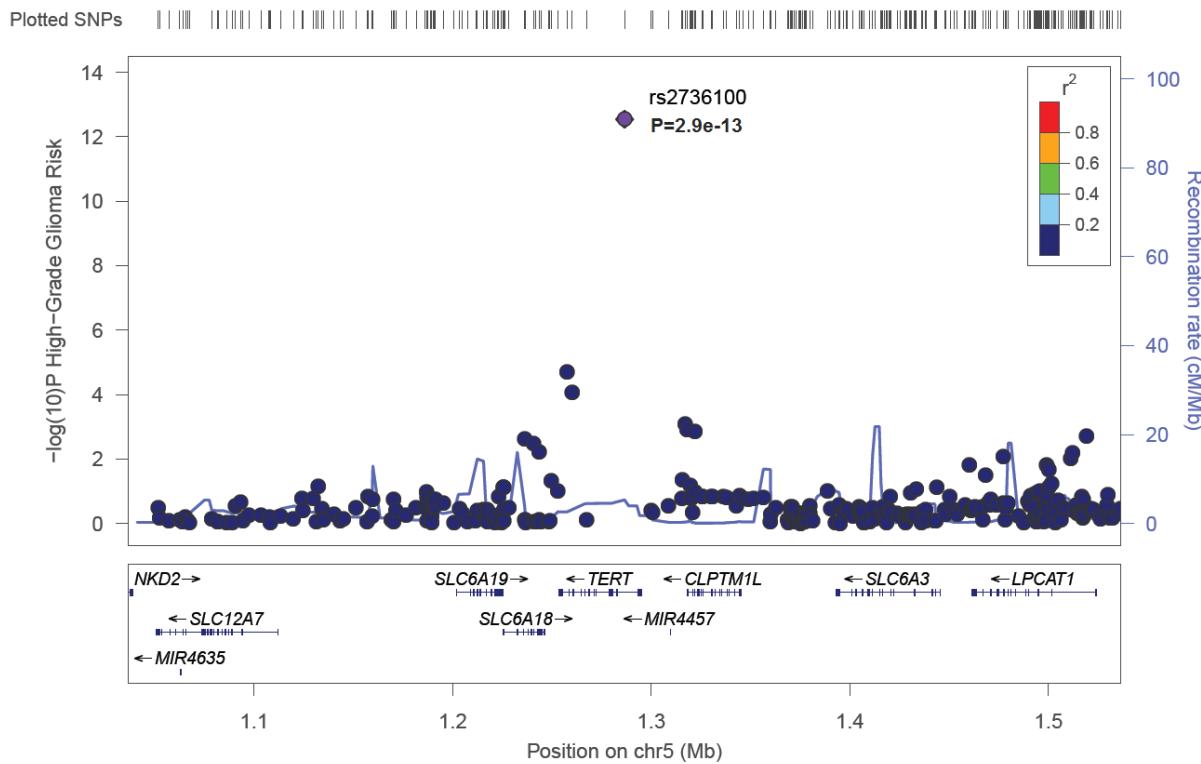
Chr3 Leukocyte Telomere Length Associations



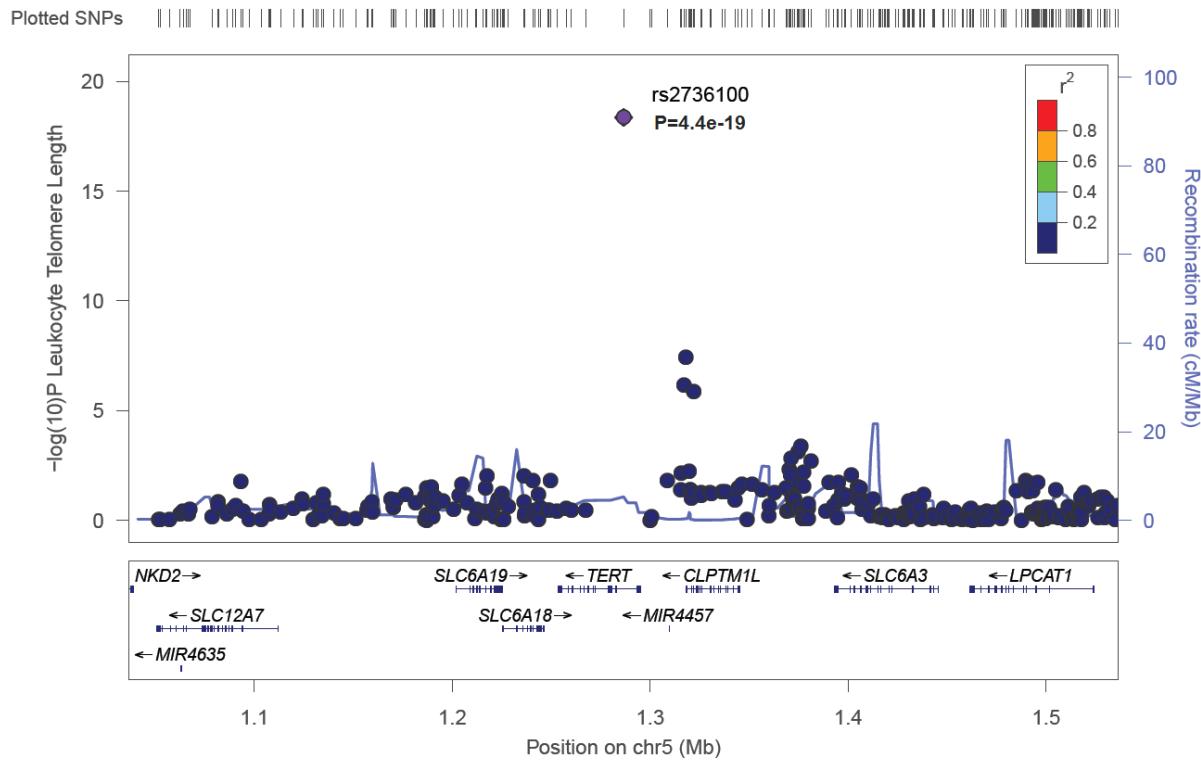
Supplementary Figure 4: SNP association plots for high-grade glioma risk (top) and mean leukocyte telomere length (bottom) at 3q26.2 (A), 5p15.33 (B) and 20q13.33 (C). The strength of linkage disequilibrium between each SNP and the high-grade glioma top hit (purple circle) is indicated by color. Recombination rates, plotted in light blue, are based on 1000 Genomes CEU samples. Black vertical bars in Supplementary Figure 3C mark the location of the RTEL1 PCNA interaction motif (PIP box).

b

Chr5 High-Grade Glioma Associations



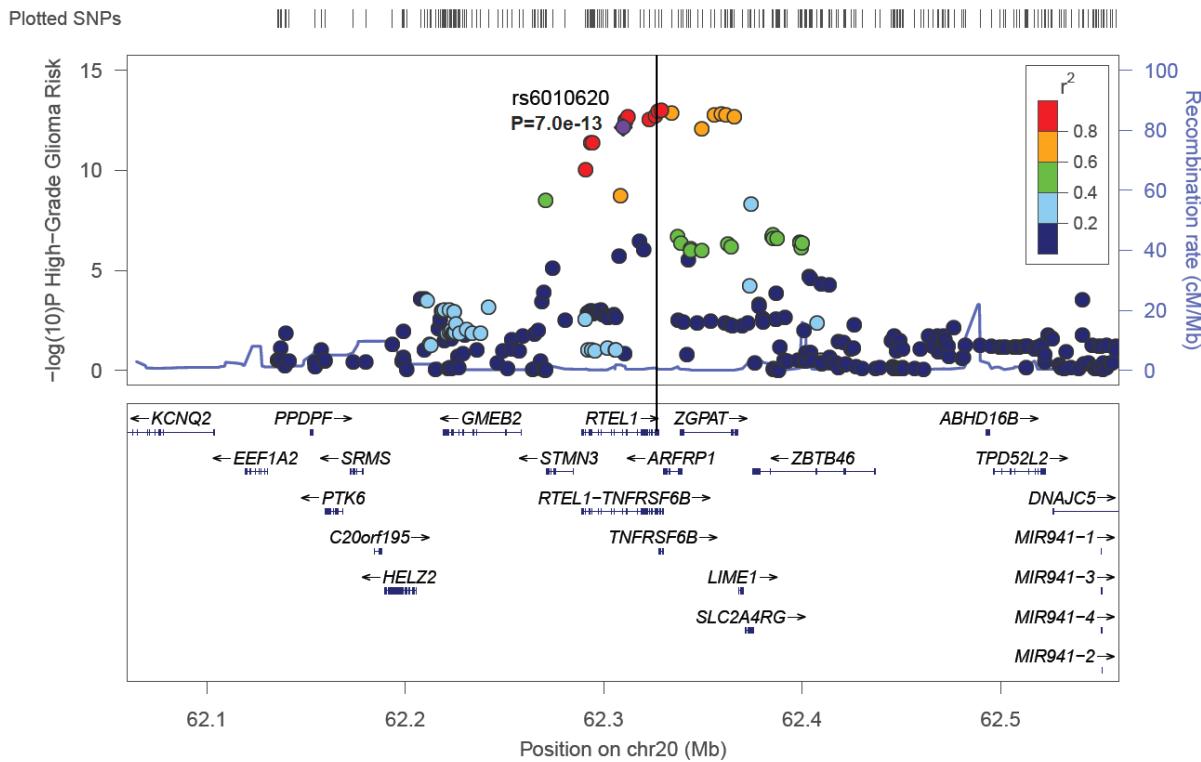
Chr5 Leukocyte Telomere Length Associations



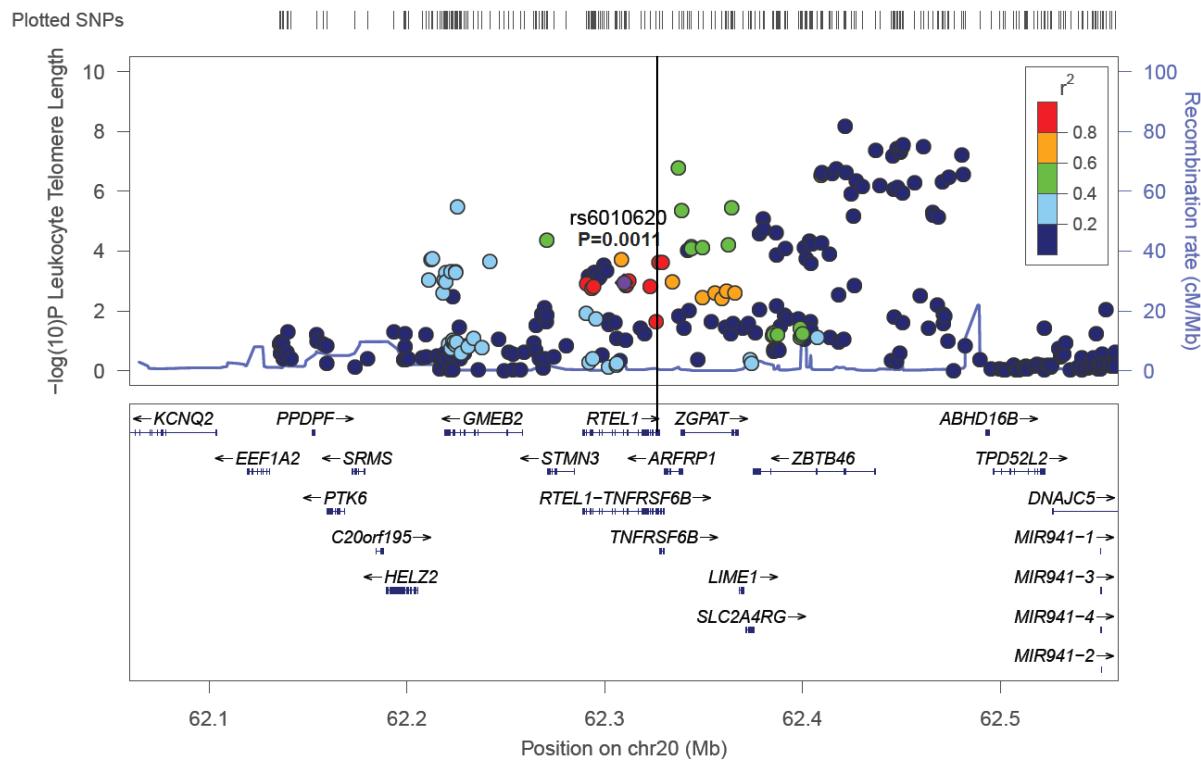
Supplementary Figure 4 (cont.): SNP association plots for high-grade glioma risk (top) and mean leukocyte telomere length (bottom) at 3q26.2 (A), 5p15.33 (B) and 20q13.33 (C). The strength of linkage disequilibrium between each SNP and the high-grade glioma top hit (purple circle) is indicated by color. Recombination rates, plotted in light blue, are based on 1000 Genomes CEU samples. Black vertical bars in Supplementary Figure 3C mark the location of the RTEL1 PCNA interaction motif (PIP box).

C

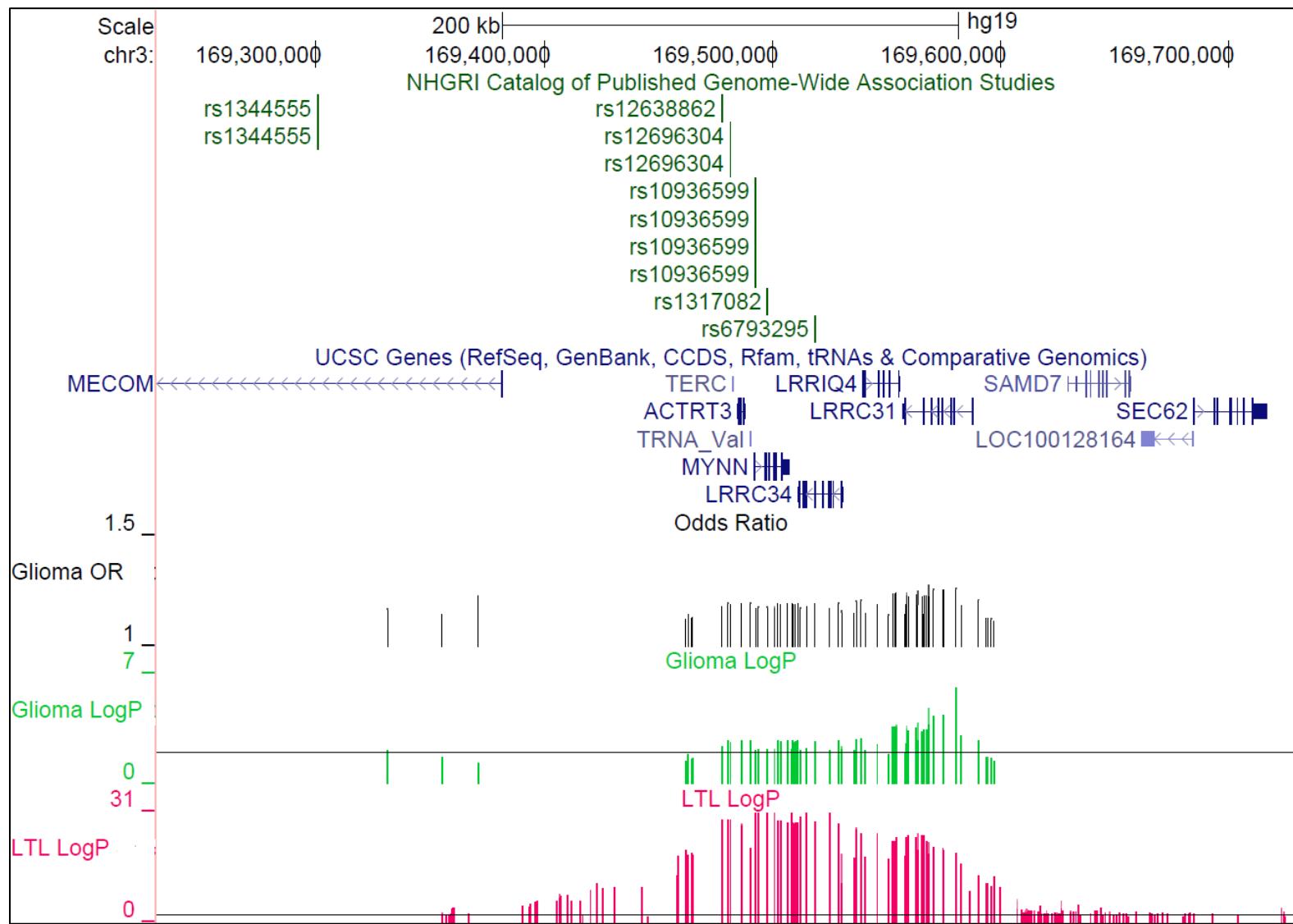
Chr20 High-Grade Glioma Associations



Chr20 Leukocyte Telomere Length Associations



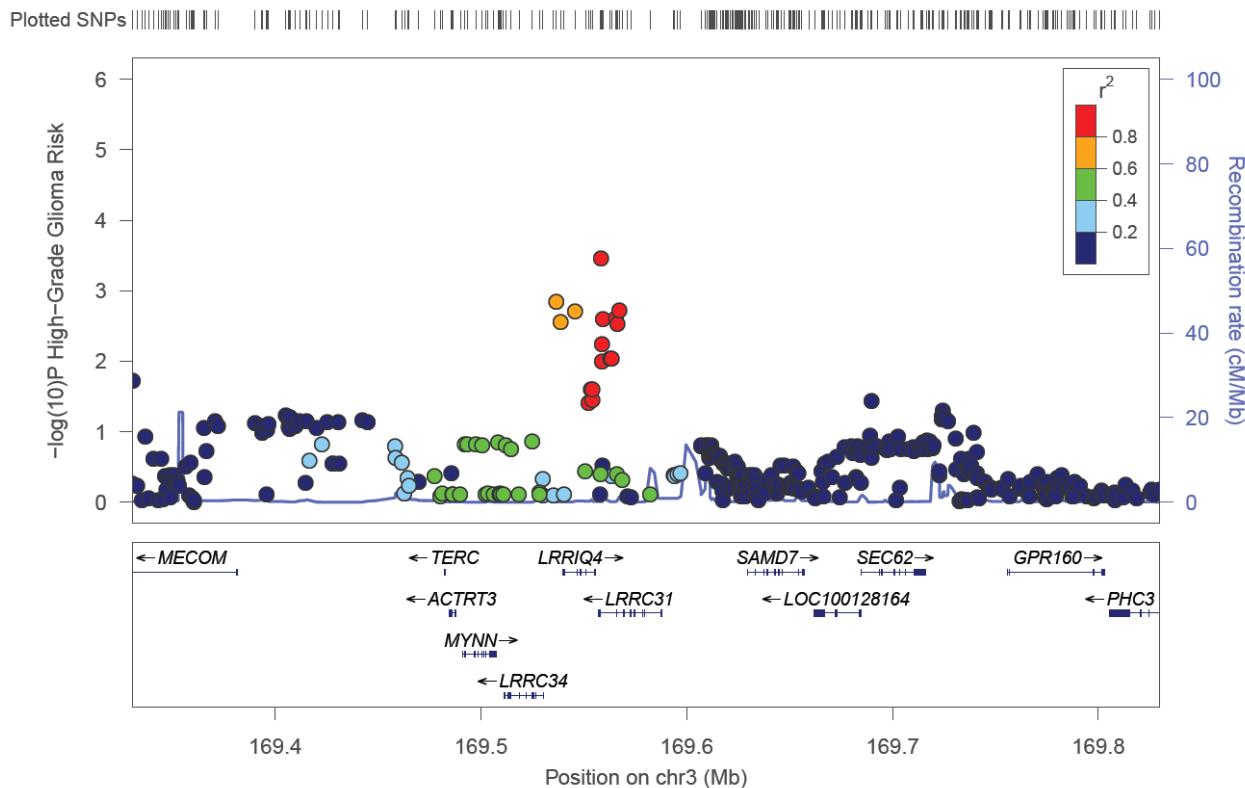
Supplementary Figure 4 (cont.): SNP association plots for high-grade glioma risk (top) and mean leukocyte telomere length (bottom) at 3q26.2 (A), 5p15.33 (B) and 20q13.33 (C). The strength of linkage disequilibrium between each SNP and the high-grade glioma top hit (purple circle) is indicated by color. Recombination rates, plotted in light blue, are based on 1000 Genomes CEU samples. Black vertical bars in Supplementary Figure 3C mark the location of the RTEL1 PCNA interaction motif (PIP box).



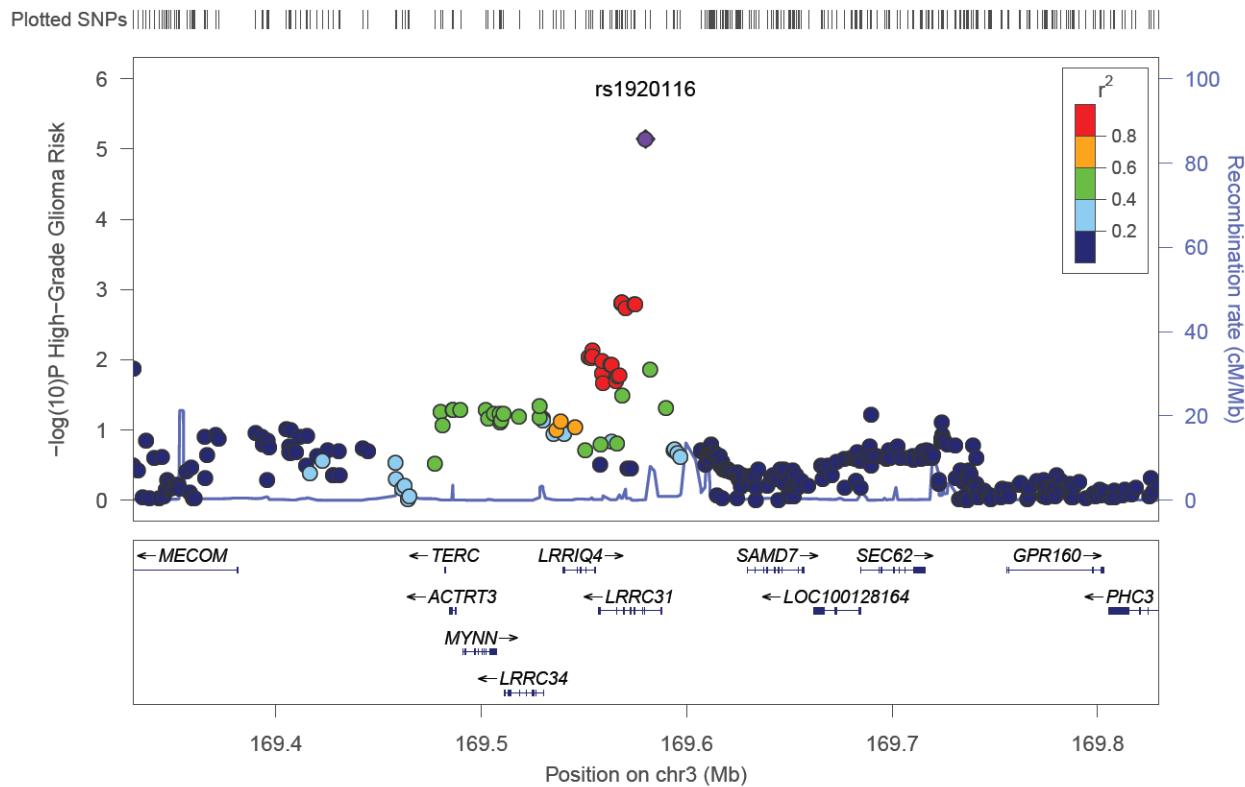
Supplementary Figure 5: Odds ratios near *TERC* for high-grade glioma risk, plotted with $-\log_{10}(P\text{-values})$ for glioma risk and mean leukocyte telomere length.

Glioma odds ratios for SNPs with $P < 0.05$ are plotted in black and correspond to the risk associated with each additional copy of the glioma risk allele. Odds ratios range from 1.11 to 1.26. $-\log_{10}(P\text{-values})$ for SNPs associated with high-grade glioma in the discovery stage ($P < 0.05$) appear in green, while $-\log_{10}(P\text{-values})$ for SNPs associated with LTL appear in pink. A horizontal black line indicates a $-\log_{10}(P\text{-value})$ of 2, corresponding to a P -value of 0.01.

Glioma Associations, Conditioned on rs1920116



Glioma Associations, Conditioned on rs10936599



Supplementary Figure 6: SNP association plots for high-grade glioma risk at 3q26.2, conditioned on lead glioma SNP rs1920116 (top) and lead LTL SNP rs10936599 (bottom). The strength of linkage disequilibrium between each SNP and rs1920116 is indicated by color. Recombination rates, plotted in light blue, are based on 1000 Genomes CEU samples.